AMENDMENTS TO THE DRAWINGS

The attached sheet of drawings includes changes to Figure 2. This sheet replaces one original drawing sheet.

Attachment: Replacement Figure 2

REMARKS

Claims 1-54 were pending in this application. Claim 2 is canceled herein. Thus, after entry of this amendment, **claims 1 and 3-54 will be pending**.

Claim 1 is amended to incorporate the limitation of claim 2. Claim 3 is amended to remove Japanese encephalitis virus from the list of recited viruses in view of the amendment to claim 1. Claim 16 is amended to recite an "isolated" cell, as required by the Office. Due to the cancellation of claim 2, claim 44 is amended to depend from claim 1. Claims 50-52 are amended to replace "about" with "at least."

The specification is amended to incorporate the substitute Sequence Listing provided herewith; to clarify the priority claim; and to insert sequence identifiers into the brief description of Figure 6. Figure 2 is amended to incorporate sequence identifiers for the amino acid and nucleotide sequences shown in the figure.

No new matter has been introduced by these amendments.

RESTRICTION REQUIREMENT

Applicant thanks the Examiner for rejoining Groups I and II and noting that the claims of Group III will be rejoined in the event of allowable subject matter.

DRAWINGS AND SEQUENCE LISTING

The Office indicates that the specification does not comply with the requirements of 37 C.F.R. §1.821 because Figure 2 contains nucleotide and amino acid sequences that were not provided with a sequence identifier. In response, Applicant submits herewith an amended Figure 2, identifying the recited sequences as SEQ ID NOs: 1-3, 10 or 11, or portions thereof. Each of the sequences shown in Figure 2 was listed in the Sequence Listing submitted at the time the application was filed.

Applicant thanks Examiner Parkin for confirming during a brief telephone conference on December 3, 2007 that the amino acid sequences shown in Figure 6 also require sequence identifiers. In response, the "Brief Description of the Drawings" section of the specification is amended to insert sequence identifiers (SEQ ID NO: 18 and 62-64) for the amino acids recited in Figure 6. A substitute Sequence Listing is also provided herewith, which includes SEQ ID NOs:

62-64. These sequences were provided in original Figure 6, therefore the amended Sequence Listing does not constitute new matter.

Thus, Applicant submits the specification is in compliance with 37 C.F.R. §1.821 and requests withdrawal of this rejection.

PRIORITY CLAIM

The Office indicates that the priority claim under 35 U.S.C. §120 is unclear and requests that the specification be amended to clearly identify those applications to which priority is claimed. The Office states the instant application has been accorded an effective filing date of April 4, 2001, based on the preliminary amendment filed July 6, 2004, and the Declaration filed with the application. In response, Applicant has amended the paragraphs on page 1, immediately following the title, to indicate that the instant application is a U.S. national stage of PCT/US02/10764, filed April 4, 2002, which claims the benefit of U.S. Patent Application 09/826,115, filed April 4, 2001. The instant application contains subject matter related to, but does not claim priority to, the remainder of the listed applications. Thus, Applicant submits the claim for priority is now clear. If the Examiner believes the priority claim is still unclear, Applicant requests that the Examiner contact the representative for Applicant listed below.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 50-52 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for the recitation of "about." Although Applicant disagrees with the Office, solely in an effort to advance prosecution, claims 50-52 are amended to replace the term "about" with "at least." Thus, Applicant submits the claims are definite and requests withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

REJECTION UNDER 35 U.S.C. §101

Claim 16 is rejected under 35 U.S.C. §101 as allegedly directed to non-statutory subject matter. The Office states that the term "cell" encompasses cells that are part of a human being. In response, claim 16 is amended herein to recited "isolated cell" as required by the Office. Accordingly, Applicant requests withdrawal of this rejection under 35 U.S.C. §101.

REJECTION UNDER 35 U.S.C. §102

Claims 1, 3, 8-10, 12 and 16 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Pletnev *et al.* (*Proc. Natl. Acad. Sci. U.S.A. 89*:10532-10536, 1992). The Office argues that Pletnev *et al.* teach isolated nucleic acids encoding chimeric flaviviruses comprising a structural protein signal sequence from a first flavivirus and an antigen from second flavivirus, and concludes this disclosure meets the limitations of the rejected claims. Applicant traverses this rejection.

As amended herein, claim 1 incorporates the limitations of claim 2, which was not included in this rejection. Thus, claim 1 is directed to an isolated nucleic acid comprising a transcriptional unit encoding a signal sequence of a structural protein of a first flavivirus and an immunogenic flavivirus antigen, wherein the antigen is of a second flavivirus or the antigen is a chimeric antigen comprising amino acid sequence from more than one flavivirus, *wherein the signal sequence is a Japanese encephalitis virus sequence.* Pletnev *et al.* do not teach or even suggest a nucleic acid wherein the signal sequence of the transcriptional unit is a Japanese encephalitis virus sequence. Thus, claim 1, and dependent claims 3, 8-10, 12 and 16, are not anticipated by Pletnev *et al.* Accordingly, Applicant requests withdrawal of this rejection under 35 U.S.C. §102(b).

REJECTION UNDER 35 U.S.C. §103

Claims 1-17, 28, 30, 32, 34, 36 and 44-54 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Yasui *et al.* (*Southeast Asian J. Trop. Med. Public Health 21(4)*:663-669, 1990) in view of Kochel *et al.* (U.S. Patent No. 6,455,509), Ivy *et al.* (U.S. Patent No. 6,136,561), Phillpotts *et al.* (*Arch. Virol. 141*:743-749, 1996) and Kozak (*J. Mol. Biol. 196*:947-950, 1987). The Office alleges it would have been obvious to one of ordinary skill in the art to prepare an expression cassette encoding the prM signal sequence and a flavivirus antigen as taught by Yasui *et al.* and to replace the antigen with immunogenic sequences from other flaviviruses as suggested by Kochel *et al.* and Ivy *et al.* The Office further states that Phillpotts *et al.* and Kozak provide the motivation to include the CMV-IE promoter and a ribosomal translational initiation sequence, respectively. Applicant traverses this rejection.

The pending claims

As recited herein, claim 1 is directed to an isolated nucleic acid comprising a transcriptional unit encoding a signal sequence of a structural protein of a first flavivirus and an immunogenic flavivirus antigen, *wherein the antigen is of a second flavivirus or the antigen is a chimeric antigen comprising amino acid sequence from more than one flavivirus*, wherein the signal sequence is a Japanese encephalitis virus sequence, and wherein the transcriptional unit directs the synthesis of the antigen. The remainder of the pending claims depend directly or indirectly from claim 1, and thus incorporate all limitations of claim 1.

Characterization of the cited references

Yasui *et al.* teach baculovirus and vaccinia virus constructs expressing Japanese encephalitis virus (JEV) proteins, such as prM and E, under the control of various promoters. In some cases, the constructs contain a JEV signal sequence. This reference reports the finding that constructs comprising the signal sequence upstream of prM or E expressed antigenically active forms of the flavivirus proteins. However, Yasui *et al.* do not teach or even suggest a construct comprising a JEV signal sequence in combination with an antigen from a different flavivirus or a chimeric flavivirus antigen.

Kochel *et al.* teach dengue virus expression constructs comprising nucleic acid sequence encoding dengue virus prM (including the signal sequence) and E proteins, the CMV enhancer and a polyA terminator. Exemplary constructs contain either dengue serotype 1 virus or dengue serotype 2 virus sequence. Kochel *et al.* discuss vaccination against each of the four dengue virus serotypes; however, this reference does not teach a nucleic acid encoding a prM signal sequence and an E protein from different dengue virus serotypes as suggested by the Office. Rather, Kochel *et al.* teach that a "tetravalent dengue DNA vaccine that provides protection against all four serotypes can be prepared by combining the four different DNA vaccines to form a tetravalent mixture" (see column 9, lines 36-39). Thus, Kochel *et al.* teach multiple transcriptional units, each comprising a signal sequence and one or more proteins from the same flavivirus. Although Kochel *et al.* state that a multivalent vaccine can be made by "cloning various combinations of the genes into one or more plasmid vectors" (see column 9, lines 39-40), the reference does not teach a signal sequence from a first flavivirus and an antigen from a second flavivirus, or a signal sequence from a first flavivirus and a chimeric flavivirus antigen, in

a single transcriptional unit. Kochel *et al.* provide no guidance or even suggestion as to how many plasmids to use or the flavivirus protein composition of each construct. Furthermore, Kochel *et al.* do not teach or even suggest a JEV signal sequence, as recited in the pending claims.

Ivy *et al.* teach expression vectors comprising nucleic acid sequence encoding a flavivirus (specifically dengue serotype 2 virus) E protein and a signal sequence. Ivy *et al.* teach that the signal sequence can be either $htPA_L$ or a "homologous" prM signal sequence. Thus, Ivy *et al.* do not teach or even suggest expression constructs wherein the signal sequence and antigenic protein are from different flaviviruses, nor does the reference teach chimeric flavivirus antigens. Furthermore, Ivy *et al.* do not teach or even suggest the use of a JEV signal sequence.

Similarly, Phillpotts *et al.* teach plasmids comprising nucleotide sequence encoding St. Louis encephalitis virus prM (including the signal sequence) and E proteins, and the CMV immediate early promoter. Phillpotts *et al.* do not teach or even suggest a JEV signal sequence, nor does the reference teach a signal sequence from a first flavivirus and an antigen from a second flavivirus, or a chimeric flavivirus antigen.

Kozak teaches a consensus ribosomal translational initiation sequence, as recited in claim 14.

The cited references do not teach or suggest each and every element of the pending claims

Each of the references cited by the Office teaches a flavivirus "transcriptional unit" in which the signal sequence is from the same flavivirus as the antigen. In addition, none of the cited references even suggests combining a signal sequence from a first flavivirus, particularly a signal sequence from JEV, with an antigen from a second flavivirus. Furthermore, none of the cited references teaches or suggests combining a signal sequence from a first flavivirus, particularly a JEV signal sequence, with a chimeric antigen comprising amino acid sequence from one or more flaviviruses.

Although the Office alleges that Kochel *et al.* teach the prM signal sequence and E protein from different dengue virus isolates, this reference teaches only constructs comprising a signal sequence and an antigen from the same dengue virus serotype. Kochel *et al.* briefly mention (see column 9, lines 36-40) a "tetravalent DNA vaccine" for eliciting immunity to all four serotypes of dengue virus; however, Kochel *et al.* teach that the tetravalent vaccine

comprises multiple plasmids, each encoding a signal sequence and antigen from a single dengue virus serotype. Kochel *et al.* state that an alternative tetravalent vaccine can be prepared "by cloning various combinations of the genes into one or more plasmid vectors," which Applicant submits is not a teaching or suggestion of a flavivirus transcriptional unit comprising a signal sequence from a first flavivirus and an antigen from a second flavivirus, or a chimeric antigen. Rather, Kochel *et al.* provide at best a vague statement about the possibility of combining dengue virus serotype-specific DNA vaccines, or portions thereof, to produce a single vaccine.

In order to establish a *prima facie* case of obviousness, the cited references must teach or suggest each and every limitation of the pending claims. Since none of the cited references, alone or in combination, even suggest using a signal sequence from a first flavivirus, particularly a JEV signal sequence, in combination with an antigen from a second flavivirus, or in combination with a chimeric antigen, the claims are not obvious.

The cited references do not provide a reasonable expectation of success

In order to establish a *prima facie* case of obviousness, a reasonable expectation of success must be found in the prior art, not in Applicant's disclosure. Since none of the cited references teach or suggest combining a signal sequence from a first flavivirus with an antigen from a second flavivirus, nor do they suggest combining a signal sequence from a first flavivirus with a chimeric antigen comprising amino acid sequence from more than one flavivirus, one of ordinary skill in the art would not have had a reasonable expectation of success for producing the claimed transcriptional units, wherein the transcriptional unit directs the synthesis of a flavivirus antigen. Only by using Applicant's specification as a guide, could one of ordinary skill in the art construct such transcriptional units.

As described by Applicant and Yasui *et al.*, the combination of signal sequence and flavivirus antigen is important for expression of an immunogenic form of the flavivirus protein. Yasui *et al.* teach that recombinant viruses lacking an appropriate signal sequence exhibited abnormal proteolytic processing, which is required to produce an immunogenic form of the flavivirus protein (see abstract). Furthermore, Applicant teaches on pages 61-65 (Example 18) of the specification that signal sequences are critical for efficient protein expression, translocation, cleavage site presentation and correct topology, which are required for production of immunogenic protein. The specification further teaches that three different vaccine constructs

differing in signal peptide sequences exhibited a difference in vaccine potential (see page 63, line 6 to page 64, line 7). In addition, Example 20 (pages 65-80 of the specification) describes the production and characterization of recombinant dengue serotype 2 virus vaccines comprising a JEV signal sequence in combination with dengue virus type 2 prM/E, or chimeric prM/E. The results demonstrated that each of the constructs exhibited a different potential for eliciting neutralizing antibodies. None of the cited references provides any guidance as to how one would construct transcriptional units comprising a JEV signal sequence in combination with a second flavivirus antigen or a chimeric antigen, wherein the transcriptional unit directs the synthesis of the antigen, as taught by Applicant's disclosure. Thus, without the teachings of the instant specification, one of ordinary skill in the art would not have had a reasonable expectation of success at constructing the flavivirus transcriptional units as claimed herein.

Summary

None of the cited references, either alone or in combination, teach or even suggest each and every limitation of the pending claims. Furthermore, one of ordinary skill in the art would have no reasonable expectation of success in view of the teachings of the cited references. Therefore, the Office has failed to establish a *prima facie* case of obviousness. Accordingly, Applicant requests withdrawal of this rejection under 35 U.S.C. §103(a).

CONCLUDING STATEMENT

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and allowance of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the representative for Applicant listed below to discuss any outstanding matters.

Respectfully submitted,

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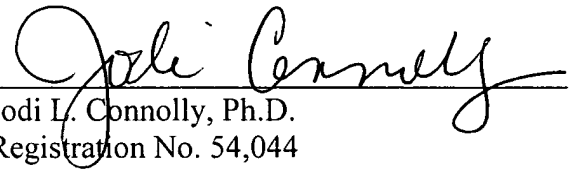
By 
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